

WHAT IS CLAIMED IS:

1. A polypeptide that inhibits signaling mediated by TNF receptor-associated factor 6 (TRAF6), wherein said polypeptide 5 comprises a TRAF6 binding domain and a leader signal sequence.

2. The polypeptide of claim 1, wherein said leader signal sequence comprises a polypeptide selected from the group consisting of Kaposi fibroblast growth factor signal sequence, HIV-1 10 Tat (48-60), D-amino acid-substituted HIV-1 Tat (48-60), arginine-substituted HIV-1 Tat (48-60), Drosophila Antennapedia (43-58), viral RNA binding peptide that comprises 7 or more arginines, DNA binding peptide that comprises 7 or more arginines and polyarginine polypeptide that has 6 to 8 arginines.

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3. The polypeptide of claim 2, wherein said viral RNA binding peptide is selected from the group consisting of HIV-1 Rev (34-50), HTLV-II Rev (4-16), brome mosaic virus Gag (7-25) and flock house virus coat protein (35-49).

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4. The polypeptide of claim 2, wherein said DNA binding peptide is selected from the group consisting of human c-Fos (139-164), human c-Jun (252-279) and yeast transcription factor GCN4 (231-252).

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5. The polypeptide of claim 1, wherein said TRAF6 binding domain is a TRAF6 binding domain from a protein selected from the group consisting of CD40, Receptor Activator of NF-κB, IL-1 receptor-associated kinase 1 (IRAK1), IL-1 receptor-associated kinase 2 (IRAK2), IRAK-M and RIP2.

10 6. The polypeptide of claim 1, wherein said TRAF6 binding domain comprises a sequence selected from the group consisting of SEQ ID NOs: 1-18.

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7. The polypeptide of claim 1, wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs: 19 and 20.

8. A method of inhibiting Receptor Activator of NF- $\kappa$ B Ligand (RANKL)-induced osteoclast differentiation, comprising the step of:

applying the polypeptide of claim 1 to osteoclast,

5 wherein inhibition of interaction between Receptor Activator of NF- $\kappa$ B and TRAF6 by said polypeptide results in inhibition of RANKL-induced osteoclast differentiation.

9. The method of claim 8, wherein said polypeptide is  
10 delivered to said cells by a mean selected from the group consisting of liposomes, a virus and a gene delivery vector.

10. The method of claim 8, wherein said osteoclast differentiation is induced by breast cancer cells.

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11. A method of inhibiting osteoclast differentiation in an individual, comprising the step of:

applying to said individual the polypeptide of claim 1, wherein inhibition of interaction between Receptor Activator of NF-

$\kappa$ B and TRAF6 by said polypeptide results in inhibition of osteoclast differentiation.

12. The method of claim 11, wherein said individual has a  
5 disease selected from the group consisting of metabolic bone disorders, leukemia, multiple myeloma, arthritis, and metastatic cancer of the bone.

13. A pharmaceutical composition comprising the  
10 polypeptide of claim 1 and a pharmaceutically acceptable carrier.

14. The composition of claim 13, wherein said polypeptide comprises TRAF6 binding domain having a sequence selected from the group consisting of SEQ ID NOs: 1-18.

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15. The composition of claim 13, wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs: 19 and 20.

16. A method of inhibiting cancer cells-induced osteolytic lesions, comprising the step of administering the composition of claim 13 to an individual.

5        17. The method of claim 16, wherein said composition is delivered to said individual by a mean selected from the group consisting of liposomes, a virus and a gene delivery vector.

10        18. The method of claim 16, wherein said cancer cells are breast cancer cells or prostate cancer cells.

15        19. A method of identifying a non-peptide small molecule capable of inhibiting interaction between receptor activator of NF-κB (RANK) and TNF receptor-associated factor 6 (TRAF6), comprising the step of:

      preparing a polypeptide comprising a TRAF6 binding domain; and

20        examining binding of TRAF6 to said polypeptide in the presence and absence of a non-peptide small molecule, wherein reduced binding in the presence of said non-peptide small molecule

would indicate that said non-peptide small molecule is capable of inhibiting RANK-TRAF6 interaction.

20. The method of claim 19, wherein said TRAF6 binding  
5 domain is derived from a protein selected from the group consisting of CD40, Receptor Activator of NF- $\kappa$ B, IL-1 receptor-associated kinase 1 (IRAK1), IL-1 receptor-associated kinase 2 (IRAK2), IRAK-M and RIP2.

10 21. The method of claim 20, wherein said TRAF6 binding domain comprises a sequence selected from the group consisting of SEQ ID NOs: 1-18.

15 22. The method of claim 19, wherein said polypeptide is immobilized on an ELISA microtiter plate.

23. The method of claim 19, wherein binding of TRAF6 to said polypeptide is determined by levels of fluorescent activities.

20 24. A non-peptide analog that mimics the function of a polypeptide comprising a TNF receptor-associated factor 6 (TRAF6)

binding domain and a leader signal sequence, wherein said polypeptide inhibits signaling mediated by TRAF6.

25. The non-peptide analog of claim 24, wherein said leader  
5 signal sequence comprises a polypeptide selected from the group  
consisting of Kaposi fibroblast growth factor signal sequence, HIV-1  
Tat (48-60), D-amino acid-substituted HIV-1 Tat (48-60), arginine-  
substituted HIV-1 Tat (48-60), Drosophila Antennapedia (43-58),  
viral RNA binding peptide that comprises 7 or more arginines, DNA  
10 binding peptide that comprises 7 or more arginines and polyarginine  
polypeptide that has 6 to 8 arginines.

26. The non-peptide analog of claim 25, wherein said viral  
RNA binding peptide is selected from the group consisting of HIV-1  
15 Rev (34-50), HTLV-II Rev (4-16), brome mosaic virus Gag (7-25) and  
flock house virus coat protein (35-49).

27. The non-peptide analog of claim 25, wherein said DNA  
binding peptide is selected from the group consisting of human c-  
20 Fos (139-164), human c-Jun (252-279) and yeast transcription  
factor GCN4 (231-252).

28. The non-peptide analog of claim 24, wherein said TRAF6 binding domain is a TRAF6 binding domain from a protein selected from the group consisting of CD40, Receptor Activator of NF- $\kappa$ B, IL-1 receptor-associated kinase 1 (IRAK1), IL-1 receptor-associated kinase 2 (IRAK2), IRAK-M and RIP2.

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29. The non-peptide analog of claim 24, wherein said TRAF6 binding domain comprises a sequence selected from the group 10 consisting of SEQ ID NOs: 1-18.

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30. The non-peptide analog of claim 24, wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs: 19 and 20.

31. A method of inhibiting Receptor Activator of NF- $\kappa$ B Ligand (RANKL)-induced osteoclast differentiation, comprising the step of:

20 applying to cells the non-peptide analog of claim 24, wherein inhibition of interaction between Receptor Activator of NF-

κB and TRAF6 by said non-peptide analog results in inhibition of RANKL-induced osteoclast differentiation.

32. The method of claim 31, wherein said osteoclast  
5 differentiation is induced by breast cancer cells.

33. A method of inhibiting osteoclast differentiation in an individual in need of such treatment, comprising the step of:

10 applying to said individual the non-peptide analog of  
claim 24, wherein inhibition of interaction between Receptor  
Activator of NF-κB and TRAF6 by said non-peptide analog results in  
inhibition of osteoclast differentiation.

34. The method of claim 33, wherein said individual has a  
15 disease selected from the group consisting of metabolic bone  
disorders, leukemia, multiple myeloma, arthritis, and metastatic  
cancer of the bone.

35. A pharmaceutical composition comprising the non-  
20 peptide analog of claim 24 and a pharmaceutically acceptable  
carrier.